February 12, 2009

Dr. C.T. Helmes
Executive Director
ETAD North America
1850 M Street, NW
Suite 700
Washington, DC 20036

Dear Dr. Helmes:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Stilbene Fluorescent Brighteners Intermediates, posted on the ChemRTK HPV Challenge Program Web site on February 8, 2006. I commend ETAD North America for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that ETAD advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. EPA has moved energetically from the HPV Challenge Program to the Chemical Assessment and Management Program, or ChAMP (www.epa.gov/champ) and is relying on Challenge chemical sponsors to provide, as expeditiously as possible, the data that are the key to this effort.

Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov. If you have any questions about this response, please contact me at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Mark W. Townsend, Chief
HPV Chemicals Branch

Enclosure

cc: O. Hernandez
R. Lee
J. Willis

**EPA Comments on Chemical RTK HPV Challenge Submission:**
**Stilbene Fluorescent Brighteners Intermediates Category**

## Summary of EPA Comments

The sponsor, the ETAD Fluorescent Whitening Agent Task Force, submitted a test plan and robust summaries to EPA for the Stilbene Fluorescent Brighteners Intermediates dated December 16, 2005. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 8, 2006. The category consists of three stilbene-2,2'-disulfonic acid derivatives. The submitter also provided data for one proposed analog.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Definition. The category definition is clear.

2. Analog and Category Justifications. (1) The proposed category approach is reasonable for ecological effects. (2) For health effects, the sharing of data between the two diamines is reasonable, as is the sharing of data between the dinitro compound and its analog. However, including the sponsored dinitro compound in a category with the diamines for the human health endpoints is inadequately supported, lacking adequate data comparability or any discussion as to how, for example, the metabolism of aromatic amines and nitro compounds will produce similar toxicological behavior in this case.

3. Physicochemical Properties and Environmental Fate. Adequate data are available for these endpoints for the purposes of the HPV Challenge program.

4. Health Effects. Adequate data were submitted for all health endpoints for the sulfonated diaminostilbenes and for the acute toxicity and gene mutation endpoints for sulfonated dinitrostilbene. EPA reserves judgment on the need to provide data for the sulfonated dinitrostilbene pending receipt of an adequate category justification or additional test data for this proposed category member.

5. Ecological Effects. Adequate data are available for these endpoints for the purposes of the HPV Challenge program.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

## EPA Comments on the Stilbene Fluorescent Brighteners Intermediates Category Challenge Submission

### Category Definition

The Stilbene Fluorescent Brighteners Intermediates Category consists of three sponsored chemicals: 4,4'-diaminostilbene-2,2'-disulfonic acid (CAS No. 81-11-8); disodium 4,4'-diaminostilbene-2,2'-disulfonate (CAS No. 7336-21-1); and disodium 4,4'-dinitrostilbene-2,2'-disulfonate (CAS No. 3709-43-1). The submitter also provided data for an analog, dipotassium 4,4'-dinitrostilbene-2,2'-disulfonate (78447-91-3).

### Category/Analog Justification

The submitter groups the three sponsored chemicals and the analog in the proposed category on the basis of similar structures, similar physical chemical and environmental fate properties, and similar toxicity profiles. The submitter further asserts that similar use, release, and exposure profiles for the proposed category members also support the category.

The chemical structures of the proposed category members and analog have a common 2,2'-stilbene-disulfonic acid backbone. Two of the sponsored chemicals are 4,4'-diamines, while the third sponsored chemical and the analog are 4,4'-dinitro compounds. The test plan states that "With respect to mammals, the category members are of low acute or repeated dose oral toxicity, are not mutagenic or clastogenic, and are not reproductive or developmental toxicants." However, the only such data for the dinitro compound is for acute and mutagenic effects, which provide only weak support for the proposed approach. While the test plan also states that the diamines are manufactured from the dinitro compounds via catalytic reduction, such synthetic interconvertibility is irrelevant to a discussion of similar toxicity. Thus, for the human health endpoints, the test plan fails to adequately support the inclusion of the dinitro compound in the category and the use of data for the diamines to characterize the dinitro compound. Similar use, release, and exposure profiles for the proposed category members do not compensate for the lack of evidence in the submission for the proposed approach. Options available to the submitter are provided below under Test Plan: Health Effects. For ecological effects, the category members and analog all have two sulfonic acid groups per structure. The data presented suggest that the high water solubility and low log P mitigate any toxicity that might otherwise result from the nitrogenous groups.

Conclusion: The submitter's approach is reasonable for ecological effects. However, without further information to support grouping the three sponsored chemicals into a single category, the category approach for health effects is supported only for evaluating the two sulfonated diaminostilbenes, with the sulfonated dinitrostilbene evaluated separately. At the current level of evidence, data from the proposed analog can be used to characterize the dinitro compound for corresponding toxicity endpoints.

**Test Plan**

Physical Chemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

Adequate data are available for these endpoints for the purposes of the HPV Challenge program.

*Water solubility*. EPA located a measured value of 39.22 g/L (one part per 25.5 parts of water) at 18°C for the dinitrostilbene disulfonic acid, disodium salt in the literature (Beilstein: Green, W., Chem. Ber., CODEN: CHBEAM, 30, <1897>, 3100). EPA recommends using this measured value rather than the submitter's read-across value from the analog, dinitrostilbene disulfonic acid potassium salt.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

Adequate data for these endpoints are available for the purposes of the HPV Challenge program.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Because the test plan did not adequately support the sharing of data among all three compounds for health effects, EPA evaluated the sponsored diaminostilbenes and the dinitrostilbene separately for the purpose of assessing health effects endpoint adequacy.

Adequate data were submitted for all health endpoints for the sulfonated diaminostilbenes and for the acute toxicity and gene mutation endpoints for the sulfonated dinitrostilbene. EPA reserves judgment on the need to provide additional data for the dinitrostilbene pending receipt of further information as discussed directly below.

The following options are available to the submitter to address the health effects endpoints for the dinitrostilbene category member: (1) provide sufficient documentation (e.g., metabolism information) to support the use of diamine data to characterize the dinitro category member for health effects; (2) perform a 28-day repeated-dose study with the dinitro category member to compare with the diamine data and confirm the read-across approach for other endpoints; or (3) perform a repeated-dose/reproductive/ developmental screen (OECD TG 422) with the dinitro category member. If the read-across approach is

not substantiated, then the submitter also needs to provide test data to assess chromosomal effects with the dinitro category member.

Ecological Effects (fish, invertebrates, and algae)

EPA reserves judgment on the adequacy of data for these endpoints pending receipt of revised robust summaries that include the missing details from the original studies. The following summary indicates the studies that, if confirmed as adequate, will adequately characterize the category for each endpoint.

*Acute Toxicity to Fish:* Adequate data for 4,4'-diaminostilbene-2,2'-disulfonic acid or for the analog 4,4'-dinitrostilbene-2,2'-disulfonic acid dipotassium salt will satisfy the endpoint.

*Acute Toxicity to Invertebrates*: Adequate data for 4,4'-diaminostilbene-2,2'-disulfonic acid will satisfy the endpoint.

*Toxicity to Algae:* Adequate data for 4,4'-diaminostilbene-2,2'-disulfonic acid will satisfy the endpoint.

*Chronic Toxicity to Invertebrates:* Adequate data for 4,4'-diaminostilbene-2,2'-disulfonic acid will satisfy the endpoint.

**Specific Comments on the Robust Summaries**

The submitter upgraded the robust summaries from an outdated OECD dossier for the major human health studies for CAS No. 81-11-8 (http://cs3-hq.oecd.org/scripts/hpv/). The submitter needs to do the same for the other SIDS endpoints for this substance (see first 20 pages of robust summaries). Robust summaries for other members of the category are also lacking in some details as noted below. The submitter should consult EPA guidance documents for the preparation of robust summaries (http://www.epa.gov/opptintr/chemrtk/pubs/general/guidocs.htm). Additionally, for robust summaries prepared from a secondary source (e.g., SIDS Dossier) the submitter should obtain original documentation of the study and prepare the robust summaries according to EPA guidance.

The submitter needs to clarify the test substance used in the biodegradation and irritation studies identified in the dossier for CAS No. 3709-43-1. These are the only data submitted for this category member and the test substance is identified as “FAT 90159/A”.

Health Effects

*Acute Toxicity.* Study details missing from the robust summaries for the several acute toxicity studies for all substances include the testing guideline, GLP compliance, test concentrations, test substance composition, statistical methods, method of administration, sex and strain, number per sex per group, whether or not necropsy was performed, duration of post-exposure observation, whether or not mortality occurred, tabulation of signs of toxicity and/or mortality by dose level and sex, and 95% confidence intervals.

Ecological Effects

*Acute Toxicity to Fish.* Study details missing from the robust summary of the fish acute toxicity study of 4,4'-diaminostilbene-2,2'-disulfonic acid include specified test concentrations, water chemistry parameters (e.g., temperature, pH, dissolved oxygen, total organic carbon [TOC]), loading, control response, mean weight and length of fish, and statistical methods used. Study details missing from the robust summary of the fish acute toxicity study of 4,4’-dinitro-2,2’-stilbenedisulfonic acid, dipotassium salt include the total organic carbon level and control response.

*Acute Toxicity to Invertebrates.* Study details missing from the robust summary of the invertebrate acute toxicity study of 4,4'-diaminostilbene-2,2'-disulfonic acid include concentrations tested, water chemistry

parameters (e.g., temperature, pH, dissolved oxygen, total organic carbon [TOC]), loading, the photoperiod, control response, age of daphnids tested, and statistical methods used.

*Toxicity to Algae.* Study details missing from the robust summary of the algae toxicity study of 4,4'-diaminostilbene-2,2'-disulfonic acid include concentrations tested, test conditions (e.g., temperature, pH, and lighting), initial cell concentrations, frequency of cell concentration quantification, control cell growth, number of replicates per concentration, statistical methods used, and 95% confidence limits of the determined $EC_{50}$.

*Chronic Toxicity to Invertebrates.* Study details missing from the robust summary of the daphnia chronic toxicity study of 4,4'-diaminostilbene-2,2'-disulfonic acid include all concentrations tested and test conditions (e.g., temperature, pH, dissolved oxygen and water hardness). The test guideline cited for the study needs to be corrected from OECD TG 202 to OECD TG 211.

**Followup Activity**

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.